REMARKS

Applicants are in receipt of the Office Action mailed August 22, 2007 and have the following remarks.

Applicants acknowledge the Examiner's indication that the objections to the Declaration and the rejection of claims 31-32 and 34-45 under 35 USC §102(b), 102(e) and 35 USC §103(a) are withdrawn, and thank the Examiner for so indicating.

Claim Rejections

I. Rejection of claims 31-32 and 34-45 pursuant to 35 U.S.C. 112(1).

Claims 31-32 and 34-45 have been rejected as allegedly violating the written description requirement; that is, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention.

In particular, the Office action points to the language "wherein the active neurotoxin possesses mouse lethality of 3.3×10^5 LD_{50}/mg or greater", which was added by amendment to claims 31 and 38 in the RCE and submission filed May 30, 2007. The Office action states that this phrase does not appear in the specification as filed or in the original claims.

Moreover, the range has no upper limit and therefore cannot be supported by two data points.

A proper written description inquiry is directed to provide an answer to the question "does the description clearly allow persons of ordinary skill in the art to recognize that he or she [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Thus, "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." Manual of Patent Examining Procedure (hereinafter "MPEP") §2163.02.

Applicants note that "[t]he examiner has the initial burden . . . of presenting evidence or reasons why a person of ordinary skill in the art would not recognize that the written description of the invention provides support for the claims." PTO FINAL EXAMINER GUIDELINES ON WRITTEN DESCRIPTION REQUIREMENT, 66 Fed. Reg. 1099, 1105 (December 29, 2000) (hereinafter the "PTO EXAMINER GUIDELINES".)

Applicants respectfully submit that the Office Action fails to provide any such reasoning or evidence. Rather, the Office Action merely makes the conclusory statements that the phrase "wherein the active neurotoxin possesses mouse lethality of 3.3×10^5 LD_{50}/mg or greater" does not appear in the specification or original claims, and that "the portion of the specification cited by Applicant provides support for only a

TeTx reconstituted with either native HC and LC or native HC and recombinant LC, but for all [sic] the active neurotoxins encompassed by the instant claims." Office Action of August 22, 2007 at page 3.

In these statements the Office action appears to have mistaken the proper standard for determining written description, articulated above, and have substituted a requirement that the claim language must contain literal, word-for-word disclosure in the specification for its language. While it is true that the specification does not contain the referenced phrase, this is clearly not required under the patent law, as MPEP §2163.02 confirms.

Far from requiring word-for-word disclosure in the specification, written description law indicates "drawings alone may provide a 'written description' of an invention as required by 35 USC 112". PTO EXAMINER GUIDELINES at 1106 and note 39, citing *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Additionally, the written description requirement may be satisfied by using such non-verbal descriptive means as structures, figures, diagrams, formulas, indeed "it is now well accepted that a satisfactory description may be in the claims or any other portion", or combination of portions, of the originally filed specification. PTO EXAMINER GUIDELINES at note 4. Obviously data contained in the application as filed is also extremely germane in determining whether a person of ordinary skill in

the relevant art would perceive the Applicants have invented the claimed subject matter.

With respect to such original disclosure, page 9, lines 23-32 of the specification indicates that active neurotoxins linked to drug molecules may be used to treat neuromuscular maladies, for example by providing a compound having a double action. In Example 4, at the paragraph bridging pages 22 and 23 the specification indicates that incubating a tetanus toxin light chain mutant having an alanine rather than a glutamic acid at amino acid position 234 with a synthetic 62 amino acid proteolytic substrate (HV62) corresponding to residues 33-94 of human VAMP-2 resulting in no detectable proteolysis. Example 4 concludes that Glu_{234} "is essential for catalytic activity" of the TeTx light chain. *Specification*, page 23, lines 1-2.

The specification as filed also states that in Clostridial neurotoxins generally, including tetanus toxin, botulinum toxin A, botulinum toxin B, botulinum toxin C, botulinum toxin D, botulinum toxin E, botulinum toxin F, and botulinum toxin G, "can be inactivated by an amino acid change in its light chain." *Specification*, Page 3, lines 20-26.

With this as background, and turning to Example 6 (pages 24 and 25, including Table 2) it can clearly be seen that the Applicants disclosed that dichain Clostridial neurotoxin reconstituted from the Ala^{234}-L chain and native H chain "had no toxic activity [described as <50 LD_{50}/mg]." Page 25, lines

20-22.(emphasis added.) However, the specification continues "the dichain reconstituted from native H chain and the recombinant L chain exhibited toxicity." Page 25, lines 20-22.

Table 2 indicates that a lethality in mice of 3.3×10^5 LD_{50}/mg is an indication of "toxicity" as this term is used in the specification. Additionally, native TeTx and the reconstituted native HC and LC, were was toxic as well, having toxicities of 0.5×10^6 and 3.3×10^6 LD_{50}/mg, respectively -- greater than the toxicity of the reconstituted native H chain and the recombinant L chain dichain. *See* Table 2.

Example 20 (page 39) of the specification shows a similar experiment using reconstituted BoNT-A HC and LA, and a BoNT light chain mutant (Tyr^{227}) lacking proteolyic activity. The assay was again the mouse lethality assay used in the previous TeTx reconstitution assay. The results of this experiment showed that "toxicity of the reconstituted wild-type recombinant dichain (6×10^7 LD^{50}/mg) was comparable to that of the dichain that had been reconstituted using native L chains (7×10^7 LD^{50}/mg)." *Specification*, page 39, lines 16-22. Moreover, "the [dichain containing the] mutated Tyr^{227} L chain is devoid of activity." *Id.* Since the mouse lethality assay of Example 6 informs that a toxicity level of 3.3×10^5 LD^{50}/mg is "active", the person of ordinary skill in the art will certainly understand that the toxicity of the dichain containing the mutated Tyr^{227} L chain in the BoNT experiment is less than this.

Moreover, the experiment of example 20 shows that the mouse lethality test is used as a measure of toxicity not just for TeTx but for other Clostridial dichain neurotoxins (such as BoNT A) having the characteristics such as cell surface binding and the specific proteolytic activities required by the pending claims.

With regard to this last point, the specification informs that the Clostridial neurotoxins are structurally and functionally similar, and that their mechanisms of toxicity are also similar. Specification, page 1. All of TeTx and the other Clostridial neurotoxins encompassed by the pending claims "induce paralysis by mechanisms that involve the inhbition of neurotransmitter release." *Id.* They are produced as single chaim toxins of about 150 KDa. *Id.* The single chain is cleaved to form an active dichain molecule having a approximately 100 KDa heavy chain and an approximately 590 KDa light chain. *Id.* In each case, the H domain contributes to the binding of the toxin to the neural cell surface, and the L chain is responsible for blocking neurotransmitter release by proteolytic cleavage of VAMP, SNAP-25, syntaxin and cellubrevin. *Id.*

Thus, the person of ordinary skill in the art would clearly understand from reading the present specification that the inventors of the presently claimed invention invented a composition comprising an active Clostridal neurotoxin having mouse lethality of 3.3×10^5 LD_{50}/mg (i.e., "active" according

to the specification) or greater (such as the native and reconstituted wild type dichain TeTx or BoNT of the Examples) joined to a neuropharmacological agent wherein the toxin binds a target host cell and cleaves SNAP-25, VAMP and cellubrevin.

In summary, Applicants respectfully submit that the August 22, 2007 Office Action did not contain the requisite evidence or reasons why a person of ordinary skill in the art would not recognize that the written description of the invention provides support for the claims, and therefore failed to meet the burden for establishing a prima facie case for unpatentability of these claims under the written description requirement of 35 USC 112(1).

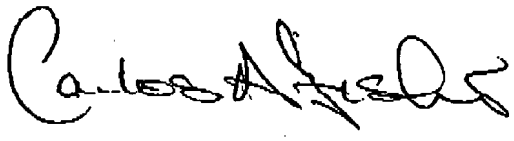
Additionally, Applicants have herein provided additional explanation and citations to the specification which conclusively demonstrates that the addition of the phrase ""wherein the active neurotoxin possesses mouse lethality of 3.3×10^5 LD_{50}/mg or greater" is amply supported by the specification. For these reasons the specification clearly would be understood to convey to the person of ordinary skill in the art that Applicants had invented the claimed compositions wherein active neurotoxin possesses mouse lethality of 3.3×10^5 LD_{50}/mg or greater.

For these reasons the Applicants respectfully request that the Examiner reconsider the present rejection and permit the pending claims to proceed to issue.

CONCLUSION

No fee is thought to be due in connection with the present response, since the end of the three-month shortened statutory period fell on November 22, 2007 (Thanksgiving, a National holiday) and this Reply is being filed on the following business day. However, if Applicants are in error in this regard kindly use Deposit Account 50-4004 for the payment of any other any charge now due, or to credit any overpayment.

Respectfully submitted,



Carlos A. Fisher
Attorney for Applicant
Reg. No. 36, 510
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (494) 450-1764